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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/686,390 | 10/15/2003 | Graham Nigel Maw | PC10343B | 6695 |

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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| EXAMINER | |
|---|---|
| MARTIN, PAUL C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1657 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/23/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/686,390 | MAW ET AL. | |
| | Examiner | Art Unit | |
| | Paul C. Martin | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *30-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/16/04,10/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 30-65 are pending in this application and were examined on their merits.

### *Information Disclosure Statement*

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or by applicant on a 1449, they have not been considered.

The information disclosure statement (IDS) submitted on 12/16/04 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner, except for the Japanese language patent which has no translation or explanation of relevance.

***Specification***

The disclosure is objected to because of the following informalities: the continuity data needs to be updated.

Appropriate correction is required.

The use of the trademarks Premarin, Cenestin and Vasomax for example, has been noted in this application (Specification, Pg. 27). These examples are not intended as a comprehensive list, but are for exemplary purposes only. All trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 30-34, 36-38, 48-52, 55 and 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18 and 30-33 of copending Application No. 10/686282. Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art at the time of the instant invention that the method of treating FSD by the step of potentiating *in vivo* cAMP with an agent in the '282 application would have encompassed the method of treating FSD by delivering a neutral endopeptidase inhibitor which causes cAMP potentiation as in the instantly claimed invention. Further, one of ordinary skill in the art would have recognized that the method of treating FSAD in Claim 30 of the '282 application, comprising the steps of orally delivering to a female suffering with FSAD an agent in an amount to cause potentiation of cAMP in the sexual genitalia of said female, wherein in the absence of sexual stimulation said agent has no or a negligible effect in causing an increase in genital blood flow and said agent has a selective effect on the genitalia is essentially the same method steps found in Claims 30-33, 36-38, 48-51, 55 and 56 in the instant application except for the use of neutral endopeptidase inhibitor instead of an agent.

The use of the terms "vaginal" or clitoral" in Claims 34 and 52 of the instant application would have been recognized by one of ordinary skill in the art as more specific definitions of the term "genital" as used in Claim 33 of the co-pending '282 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the instant application, the disclosure fails to provide information that would allow one of ordinary skill in the art at the time of the instant invention to practice the claimed invention without undue experimentation.

The entire invention encompassed by the claims (30-65) has not been enabled because:

1. Quantity of experimentation necessary would be undue because of the large proportion of inoperative compounds claimed.

With respect to the adequacy of disclosure that a claimed genus possesses an asserted utility, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if it would be deemed likely by one skilled in the art, in view of contemporary knowledge in the art, that the claimed genus would possess the asserted utility. In re Oppenauer, 31 CCPA 1248, 143 F.2d 974, 62 USPQ 297; In re Cavallito et al., 48 CCPA 711, 282F.2d 357, 127 USPQ 202. For both adequate disclosure and/or enablement requires representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim possess the alleged utility and additionally demonstrate that applicant had possession of the full scope of the claimed invention. See In re Riat et al. CCPA 1964 327 F2d 685, 140 USPQ 471; In re Barr et al. CCPA 1971 444 F2d 349, 151 USPQ 724, for enablement and for disclosure see Court of Appeals for the Federal Circuit decision, The Regents of the University of California v. Eli Lilly and Company which can be found at the Federal Circuit web site, www.fedcir.gov as file 96-1175.

The instant disclosure does not indicate or otherwise provide any data or other indication as to what specific inhibitors were tested and found to have the claimed activity of inhibiting NEP.

The instant example (Specification Pgs. 130 and 131), is directed to a generic screening assay in an animal model with no indication as to which of the laundry list of I:NEP (Specification at pages 79-86) actually worked in the assay. Many of the cited NEP inhibitors found in the instant disclosure are lacking in name or structures, casting doubt on the Applicant's actual in-hand possession of all of these inhibitors. The instant Drawings similarly lack any indication as to which inhibitor's data is being displayed. The generic screening assay is directed to specific selective inhibitors of a very specific NEP identified by an EC number and SEQ ID NO: 1, however the instant invention is drawn to a method compsising any inhibitor of any unspecified neutral endopeptidase with no specific data or examples indicating that there is any cause and effect inhibition between any one of the myriad of inhibitors claimed and the multiple types of neutral endopeptidase found throughout (at the very least) other mammals.

2. Amount of direction or guidance presented is insufficient to predict which substances encompassed by the claims would work.

The Applicant provides numerous citations of references which (presumably) are directed, in some form, toward the manufacture and/or use of I:NEP. The Applicant states that all of these compounds were prepared, tested and found to potentiate cAMP and therefore are concluded to be useful in treating FSAD. However, the fact that a particular compound may possess a particular property, such as potentiating cAMP, does not however indicate that said compound would be effective or useful in the treatment of a particular disorder. The Applicant's scope is drawn to the treatment of any example of FSD a complex disorder with a pathology beyond the narrow scope of inhibiting a particular enzyme. Berman *et al.* (1999) indicates that FSD can be classified into at least 4 Groups, of which FSAD is only one, and that FSAD physical symptoms occurs largely secondarily to psychological factors (Pg. 385, Column 2, Lines 28-40). Further, Applicant has provided no data or proof that any specific I:NEP was tested on a specific NEP and actually possessed the claimed activity.

3. Presence of working examples are only for generic substances and extension to other compounds has not been specifically taught or suggested.

Working examples in the instant disclosure are of a general nature, with specific inhibition data for all of the claimed I:NEP compounds not being shown, and the further application of those compounds toward treatments of FSD is of a prophetic nature.

The listing of compounds with some alleged I:NEP activity and a generic screening assay is not sufficient proof that the Applicant did indeed have a working NEP inhibitor with a defined structure/function relationship in inhibiting the NEP disclosed as EC 3.4.24.11 (SEQ ID NO: 1) as claimed.

4. The nature of the invention is complex and unpredictable.

Claims drawn to pharmaceuticals and methods of treatment generally require supporting data because of the unpredictability in biological responses to therapeutic treatments. For the efficacy of a drug treatment *in vivo* faces unfavorable obstacles not present in *in vitro* models. As such, *in vivo* utility necessarily involves unpredictability with respect to physiological activity of an asserted process in humans. See discussion in Ex parte Kranz, 19 USPQ 2d 1216, 1218-1219 (6/90). For examples, drug delivery to the target area must survive the acidic environment of the stomach if administered orally. Additionally, the delivery of the drug across necessary cell surfaces in amounts needed to be efficacious, but not lethal to the subject, necessitates sensitive testing in order to adequately determine the proper human dosage.

5. State of the prior art.

Physiologic treatments of FSD in humans varies from patient to patient with hormonal therapy to the administration of drugs such as sildenafil, apomorphine and phentolamine, all treatments involving other pathways not involving neutral endopeptidase inhibition (Berman (1999), Pgs. 389-90).

6. Breadth of the claims encompasses an innumerable number of compounds and disorders.

Accordingly, in the present instance, the claimed invention encompasses a veritable plethora of possible compounds of diverse structure and type (See Specification Pgs. 80-86) and the use thereof as a pharmaceutical for treating a wide variety of physiological and psychological conditions. The inadequate disclosure coupled with a lack of representative examples and the art recognized unpredictability with respect to the effects of bioactivity of making even subtle changes to the chemical structure of the underlying compounds, thus preclude the making and use of compounds within the scope of the presently claimed invention by the skilled artisan without undue experimentation.

In re Wands, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Also, due to the unpredictability of the chemical and biotechnological arts the extension of the substances provided in the working examples of the specification to other inhibitors or NEP enzymes is highly uncertain. There is no direction to determine the optimum combination and selection of compounds.

Claims 39-46 and 57-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim.

In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus.

See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

In the instant case, the claims are drawn to a neutral endopeptidase inhibitor with Ki values of less than about 100nm, 75nm, 50nm, 25nm, 20nm, 15nm, 10nm and 5nm.

*(1) Level of skill and knowledge in the art:*

Those of ordinary skill in the art would have recognized that Ki values are very specific for inhibitor/enzyme combinations. Even subtle changes in either an enzyme or inhibitor structure can result in fluctuation in the kinetic parameters of an enzyme reaction. For example, Hersh *et al.* (1986) discloses the extreme variability of Ki values of 8 pairs of closely related inhibitors, varying only in amide groups, on a mammalian NEP (Pg. 6436, Table III).

*(2) Partial structure:*

Applicant has provided numerous examples of NEP inhibitors and the structures thereof, however it cannot be determined which inhibitors actually possess the claimed activity and whether or not the Applicant indeed had possession of those specific inhibitors and that those inhibitors exhibited NEP Ki values in the claimed ranges.

*(3) Physical and/or chemical properties:*

As it cannot be determined which specific NEP inhibitors are claimed and were examined in the working examples, the physical and chemical properties are likewise undisclosed in the instant disclosure.

*(4) Functional characteristics:*

As above, the functional characteristics of the NEP inhibitor cannot be determined as the teachings of the instant disclosure do not indicate which inhibitors were tested, which had the claimed functions and, which if any, inhibitor the claimed invention is directed to.

*(5) Method of making the claimed invention:*

The instant invention falls short of providing the necessary information to allow one of ordinary skill in the art to determine what specific NEP inhibitor is being claimed, only that one (or more) of a long list of inhibitors exhibits some activity toward NEP and presumably that the undisclosed inhibitor has a similarly undisclosed Ki value toward an NEP.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Claims 30 and 48 are broadly generic to all possible neutral endopeptidase inhibitors encompassed by the claims. The possible variations are enormous to any class of enzyme inhibitor. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of an NEP inhibitor beyond those disclosed in the non-specific examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of which inhibitors actually had the claimed activity.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 31 and 49 indicate that the I:NEP inhibitor will have a selective effect on the genitalia of the female subject the inhibitor is being delivered to. It is unclear what the metes and bounds of a selective effect would encompass, selective being open to interpretation and not specifically defined in the instant disclosure. It would appear that as NEP is found in other tissues beyond those of the genitalia that the desired effect would preferentially be highly selective.

For example, Claims 32 and 50 indicate that the inhibitor will have little or no effect in causing (the very specific effect) of increasing genital blood flow in the absence of sexual stimulation (specific condition).

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

3/30/07

JON WEBER
SUPERVISORY PATENT EXAMINER